

# **Nitrogen-containing bisphosphonates are associated with reduced risk of pneumonia in patients with hip fracture**

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## **Supplementary Method**

### **Description of time-dependent PS matching approach**

To estimate the PS, covariates including age, sex, year of index date, nursing home residency, surgery operation for hip fracture, admission hospital, usage of clinical services, history of pneumococcal/seasonal influenza vaccination, comorbidities, and recent medication records (within 180 days on or before index date) classified by British National Formulary category were included in the model. (Table S1)

First, we divided the period from the date of discharge to the end of study into 1-month blocks. At each time block, we estimated the PS based on the patients' characteristics during the time block using logistic regression models. Within each time block, we matched patients treated with N-BP to patients who had not yet received any N-BP treatment based on their PS at the time block. The matched pairs were followed from the time block until the occurrence of a pneumonia event, switch to another anti-osteoporosis medication, death, or end of follow up, whichever occurred first.

Table S1. List of covariates included in the propensity score model

<b>Demographics</b>	
Sex	
Age	
Year on index date	
<b>Clinical care</b>	
Surgery operation for hip fracture	
Nursing home residency	
History of pneumococcal / seasonal influenza vaccination	
Admission hospital of the hip fracture episode	
Number of visits in out-patient clinics in the past one year	
Number of admission to hospital in the past one year	
Number of visits in intensive care unit in the past one year	
<b>Medical history</b>	<b>ICD9 Codes</b>
<i><b>Respiratory related diseases</b></i>	
Chronic obstructive pulmonary disease, asthma, and bronchiectasis	490-496, 500-505, 506.4
History of pneumonia	481, 482, 483, 485, 486
Other lung diseases	460-466, 470-478, 510-519
<i><b>Cardiovascular diseases</b></i>	
Coronary heart disease	410, 411, 412, 413, 414, 429.2, 429.71, 429.79
Congestive Heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428
Cerebrovascular diseases	430-437
Hypertensive diseases	401-405
Arrhythmia and conduction disorders	426-427
Arterial disease	433.00, 433.10, 433.20, 433.30, 433.80, 433.90, 440-445, 447
<i><b>Endocrine and metabolic disorders</b></i>	
Overweight and obesity	278.0
Hyperlipidaemia	272.0-272.2, 272.4
Diabetes	250
Thyroid disorders	242-244
<i><b>Renal diseases</b></i>	
Chronic renal disease	403, 404, 582, 585, 590.0
<i><b>Liver diseases</b></i>	
Esophageal varices, chronic liver disease, hepatic failure, cirrhosis	456.0, 456.1, 456.2, 571.2, 571.4, 571.5, 571.6, 572.2, 572.3, 572.4, 572.8
<i><b>Bone related diseases</b></i>	
Osteoporosis	733.0
Major fractures other than hip fracture	805, 812, 813, 814
<i><b>Other diseases</b></i>	
Dementia	290
Connective tissue disease	710.0, 710.1, 710.4, 714.0, 714.1, 714.2, 714.81, 725

History of Fall

781.2, 781.3, 781.99, V15.88, E880, E881, E882,  
E883, E884, E885, E886, E888

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<b>Prescription drug in the past 180 days</b>	<b>BNF category</b>
Proton-pump inhibitors	BNF 1.3.5
Cardiac glycosides	BNF 2.1.1
Loop diuretics	BNF 2.2.2
Other diuretics	BNF 2.2.1 / 2.2.3 / 2.2.4 / 2.2.5
Anti-arrhythmics class I and II	BNF 2.3.2
Beta-blockers	BNF 2.4
Angiotensin II receptor blockers / Angiotensin-converting enzyme-I	BNF 2.5.5.1 / 2.5.5.2 /2.5.5.3
Nitrates	BNF 2.6.1
Calcium channel blockers	BNF 2.6.2
Peripheral vasodilators	BNF 2.6.4
Anticoagulants	BNF 2.8
Platelet inhibitors	BNF 2.9
Lipid regulating drugs	BNF 2.12
Beta2-agonists	BNF 3.1
Inhaled corticosteroids	BNF 3.2
Antipsychotics	BNF 4.2
Antidepressants	BNF 4.3
Insulins	BNF 6.1.1
Antidiabetic drugs	BNF 6.1.2
Oral corticosteroids	BNF 6.3 *only oral/injection/parenteral
Immunosuppressant	BNF 8.2
Nonsteroidal anti-inflammatory drugs	BNF 10.1.1

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Table S2. Baseline characteristics of propensity score matched cohort (Non-N-BP anti-osteoporosis medication vs. N-BPs).

	Matched cohort		
	Non-N-BP anti-osteoporosis medications	N-BPs*	ASD^
Subject, n (%)	507	1,284	
Male, n (%)	92 (18.1)	263 (20.5)	0.06
Age, mean (SD)	82.2 (7.95)	81.9 (7.49)	0.05
50-69	39 (7.7)	79 (6.2)	
70-89	378 (74.6)	1027 (80.0)	
90+	90 (17.8)	178 (13.9)	
Year of index date, n (%)			0.08
2005	8 (1.6)	13 (1.0)	
2006	11 (2.2)	26 (2.0)	
2007	27 (5.3)	72 (5.6)	
2008	42 (8.3)	106 (8.3)	
2009	52 (10.3)	131 (10.2)	
2010	61 (12.0)	148 (11.5)	
2011	47 (9.3)	141 (11.0)	
2012	50 (9.9)	121 (9.4)	
2013	54 (10.7)	131 (10.2)	
2014	54 (10.7)	134 (10.4)	
2015	62 (12.2)	159 (12.4)	
2016	39 (7.7)	102 (7.9)	
Admission hospital cluster, n (%)			0.10
Hong Kong West Cluster	35 (6.9)	102 (7.9)	
Hong Kong East Cluster	100 (19.7)	247 (19.2)	
New Territories West Cluster	42 (8.3)	85 (6.6)	
New Territories East Cluster	96 (18.9)	274 (21.3)	
Kowloon West Cluster	59 (11.6)	164 (12.8)	

Kowloon East Cluster	120 (23.7)	282 (22.0)	
Kowloon Central Cluster	55 (10.8)	130 (10.1)	
Nursing home residency, n (%)	84 (16.6)	190 (14.8)	0.05
Seasonal influenza / Pneumococcal vaccination, n (%)	91 (17.9)	236 (18.4)	0.01
Surgical operation for hip fracture, n (%)	484 (95.5)	1,243 (96.8)	0.07
Frequency of healthcare service in past one year, mean (SD)			
In-patient admission	1.63 (1.55)	1.49 (1.29)	0.09
Out-patient clinics	13.8 (14.4)	13.6 (13.4)	0.02
Intensive care units	<0.01 (0.06)	0.01 (0.07)	0.02
Medical history, n (%)			
Coronary heart disease	59 (11.6)	172 (13.4)	0.05
Congestive heart failure	47 (9.3)	123 (9.6)	0.01
Arrhythmia and conduction disorders	62 (12.2)	159 (12.4)	0.01
Arterial disease	22 (4.3)	59 (4.6)	0.01
Hypertensive disease	232 (45.8)	585 (45.6)	<0.01
Cerebrovascular disease	81 (16.0)	202 (15.7)	0.01
Chronic obstructive pulmonary disease	47 (9.3)	117 (9.1)	0.01
Other lung diseases	111 (21.9)	253 (19.7)	0.05
Diabetes	135 (26.6)	308 (24.0)	0.06
Hyperlipidemia	64 (12.6)	172 (13.4)	0.02
Renal failure	21 (4.1)	38 (3.0)	0.06
Osteoporosis	74 (14.6)	181 (14.1)	0.01
Fall	500 (98.6)	1,252 (97.5)	0.08
Other major fractures	92 (18.1)	218 (17.0)	0.03
Dementia	26 (5.1)	53 (4.1)	0.05
Thyroid disorders	24 (4.7)	40 (3.1)	0.08
Prescription in past 180 days, n (%)			
Digoxin	9 (1.8)	43 (3.3)	0.10
Loop diuretics	62 (12.2)	170 (13.2)	0.03
Other diuretics	33 (6.5)	91 (7.1)	0.02
Anti-arrhythmics class I and II	8 (1.6)	24 (1.9)	0.02

Beta blockers	101 (19.9)	258 (20.1)	<0.01
Angiotensin receptor blocker/ angiotensin converting enzyme inhibitor/ renin inhibitor	126 (24.9)	313 (24.4)	0.01
Nitrates	53 (10.5)	125 (9.7)	0.02
Calcium channel blockers	194 (38.3)	471 (36.7)	0.03
Anticoagulants	23 (4.5)	70 (5.5)	0.04
Platelet inhibitors	141 (27.8)	358 (27.9)	0.00
Lipid regulating drugs	90 (17.8)	220 (17.1)	0.02
Antipsychotics	30 (5.9)	75 (5.8)	<0.01
Antidepressants	50 (9.9)	97 (7.6)	0.08
Antidiabetic drugs	107 (21.1)	244 (19.0)	0.05
Oral corticosteroids	26 (5.1)	76 (5.9)	0.04
Non-steroidal anti-inflammatory drugs	60 (11.8)	149 (11.6)	0.01
Proton pump inhibitors	71 (14.0)	150 (11.7)	0.07
Beta2 agonists	52 (10.3)	116 (9.0)	0.04
Inhaled corticosteroids	29 (5.7)	66 (5.1)	0.03

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\*N-BPs nitrogen-containing bisphosphonates

^Absolute standardized difference compared with non-N-BP anti-osteoporosis medications exposed group

Table S3. Subgroup analysis: Risk of pneumonia in patients treated with N-BPs after hip fracture, compared with no treatment, stratified by sex, and vaccination

Sub-group	Exposure group	Subject, n	Event, n	Incidence / Mortality rate, per 100 person-years	Hazard ratio <sup>c</sup> (95% CI)	P
<b>Incident pneumonia</b>						
Female	Non-exposed	9,096	2,598	8.3 (7.9-8.6)	1	-
	All N-BPs <sup>a</sup>	3,113	687	6 (5.6-6.5)	0.74 (0.66-0.81)	<0.001
	Alendronate	2,507	497	5.8 (5.3-6.4)	0.74 (0.66-0.84)	<0.001
Male	Non-exposed	2,694	956	11 (10.3-11.7)	1	-
	All N-BPs	928	290	10.3 (9.2-11.6)	0.78 (0.65-0.94)	0.009
	Alendronate	791	235	10 (8.8-11.4)	0.84 (0.71-0.99)	0.037
Vaccination <sup>b</sup>	Non-exposed	1,839	515	11.4 (10.5-12.5)	1	-
	All N-BPs	637	137	8.2 (6.9-9.7)	0.73 (0.58-0.92)	0.007
	Alendronate	543	108	7.8 (6.4-9.4)	0.69 (0.53-0.89)	0.004
No vaccination	Non-exposed	9,943	3,095	8.8 (8.5-9.1)	1	-
	All N-BPs	3,404	840	6.7 (6.3-7.2)	0.79 (0.72-0.86)	<0.001
	Alendronate	2,755	624	6.6 (6.1-7.1)	0.78 (0.7-0.87)	<0.001
<b>Pneumonia mortality</b>						
Female	Non-exposed	9,096	1,080	3.1 (2.9-3.3)	1	-
	All N-BPs	3,113	232	1.9 (1.6-2.1)	0.62 (0.52-0.74)	<0.001
	Alendronate	2,507	173	1.9 (1.6-2.2)	0.68 (0.55-0.82)	<0.001
Male	Non-exposed	2,694	453	4.6 (4.2-5.1)	1	-
	All N-BPs	928	122	3.9 (3.3-4.7)	0.75 (0.58-0.96)	0.025
	Alendronate	791	97	3.8 (3-4.6)	0.66 (0.49-0.87)	0.004



	Non-exposed	1,839	190	3.8 (3.3-4.3)	1	-
Vaccination	All N-BPs	637	48	2.6 (1.9-3.5)	0.67 (0.44-1.01)	0.055
	Alendronate	543	39	2.6 (1.8-3.5)	0.71 (0.45-1.12)	0.136
	Non-exposed	9,943	1,363	3.5 (3.3-3.7)	1	-
No vaccination	All N-BPs	3,404	306	2.2 (2-2.5)	0.65 (0.56-0.76)	<0.001
	Alendronate	2,755	231	2.3 (2-2.6)	0.65 (0.54-0.77)	<0.001

a N-BPs included alendronate, ibandronate, risedronate, and zoledronate

b Patients received seasonal influenza vaccine in the past one year or pneumococcal vaccine on/before index date.

c Models were adjusted for imbalanced variables (year of index date, frequency of in-patients admission , use of anticoagulants and non-steroidal anti-inflammatory drugs in the past 180 days)

Table S4 Sensitivity analysis of patients treated with N-BPs after hip fracture.

Sensitivity analysis	Outcome	Group	Subject, n	Event, n	Incidence / Mortality rate, per 100 person-years	Hazard ratio <sup>c</sup> (95% CI)	P
Exclude patients with late treatment <sup>a</sup>	Incident pneumonia	Non-exposed	8,384	2,667	9.4 (9.1-9.8)	1	-
		All N-BPs	2,810	716	7 (6.5-7.6)	0.74 (0.67-0.82)	<0.001
		Alendronate	2,259	526	6.8 (6.3-7.5)	0.71 (0.64-0.8)	<0.001
	Pneumonia mortality	Non-exposed	8,384	1,160	3.7 (3.5-3.9)	1	-
		All N-BPs	2,810	261	2.3 (2.1-2.6)	0.66 (0.56-0.77)	<0.001
		Alendronate	2,259	195	2.3 (2-2.7)	0.63 (0.52-0.76)	<0.001
IPTW <sup>b</sup> analysis, compared with no treatment	Incident pneumonia	Non-exposed	40,985	15,747	12.1 (11.9-12.3)	1	-
		All N-BPs	5,653	1,402	7.1 (6.7-7.5)	0.76 (0.72-0.81)	<0.001
		Alendronate	4,528	1,036	7 (6.6-7.4)	0.75 (0.7-0.8)	<0.001
	Pneumonia mortality	Non-exposed	40,985	7,584	5.1 (4.9-5.2)	1	-
		All N-BPs	5,653	489	2.2 (2-2.5)	0.60 (0.55-0.66)	<0.001
		Alendronate	4,528	366	2.3 (2-2.5)	0.60 (0.54-0.67)	<0.001
IPTW analysis, compared with non-N-BPs anti-osteoporosis medication	Incident pneumonia	Non-N-BPs	604	195	15.1 (13.1-17.4)	1	1
		All N-BPs	5,643	1,396	7.1 (6.7-7.4)	0.52 (0.44-0.61)	<0.001
		Alendronate	4,528	1,036	7 (6.6-7.4)	0.51 (0.44-0.6)	<0.001
	Pneumonia mortality	Non-N-BPs	604	92	6.1 (4.9-7.5)	1	1
		All N-BPs	5,643	486	2.2 (2-2.4)	0.38 (0.30-0.47)	<0.001
		Alendronate	4,528	366	2.3 (2-2.5)	0.38 (0.30-0.49)	<0.001

a Late treatment was defined as patient receiving first prescription of N-BPs after 180-days post discharge

b Inverse probability of treatment weighting using propensity score

c Models in PS matching were adjusted for imbalanced variables (year of index date, frequency of in-patients admission, use of anticoagulants and non-steroidal anti-inflammatory drugs in the past 180 days)

Table S5. Risk of injury and trauma in patients treated with N-BPs after hip fracture, compared with no treatment

Group	PS matching					IPTW				
	Subject, n	Event, n	Incidence, per 100 person-years (95% CI)	Hazard ratio (95% CI)	P	Subject, n	Event, n	Incidence, per 100 person-years (95% CI)	Hazard ratio (95% CI)	P
Non-exposed	12,365	123	0.3 (0.2-0.3)	1	-	40,985	504	0.3 (0.3-0.4)	1	-
All N-BPs	4,131	38	0.2 (0.2-0.3)	0.81 (0.51-1.27)	0.35	5,653	73	0.3 (0.3-0.4)	1.08 (0.83-1.39)	0.57
Alendronate	3,366	31	0.3 (0.2-0.4)	0.79 (0.47-1.33)	0.32	4,528	57	0.4 (0.3-0.5)	1.16 (0.88-1.54)	0.30

“Injury and trauma” was used as a negative control outcome as it should be unrelated to pneumonia or influenza infection.<sup>1</sup>

ICD9 codes for Injury and trauma included E800 - E848; E860 - E869; E890 - E899; E900 - E909; and E910 - E915.

Table S6. Risk of pneumonia in unmatched cohort using a fully adjusted model<sup>^</sup> (patients treated with N-BP vs no treatment)

	Hazard ratio <sup>^</sup> (95% CI)	
	Incident pneumonia	Pneumonia mortality
N-BPs treatment	0.77 (0.73-0.82)	0.64 (0.58-0.71)
Sex		
Female	Reference	Reference
Male	1.1 (0.98-1.23)	2.24 (2.14-2.35)
Age	1.06 (1.06-1.06)	1.08 (1.07-1.08)
Year of index date		
2005	Reference	Reference
2006	1.05 (0.98-1.13)	0.99 (0.9-1.08)
2007	1.1 (1.03-1.18)	1.06 (0.97-1.17)
2008	1.06 (0.99-1.14)	1.02 (0.92-1.12)
2009	1.11 (1.04-1.19)	1.03 (0.93-1.14)
2010	1.07 (0.99-1.15)	1 (0.91-1.11)
2011	0.99 (0.92-1.07)	0.91 (0.82-1.01)
2012	0.93 (0.86-1.0)	0.9 (0.81-1.01)
2013	0.96 (0.89-1.04)	0.92 (0.82-1.03)
2014	1.15 (1.06-1.24)	0.96 (0.84-1.09)
2015	1.24 (1.12-1.36)	1.18 (1.01-1.37)
2016	1.15 (0.88-1.51)	1.19 (0.76-1.86)
Admission hospital cluster, n (%)		
Hong Kong East Cluster	Reference	Reference
Hong Kong West Cluster	0.99 (0.93-1.06)	1 (0.9-1.11)
New Territories West Cluster	0.98 (0.93-1.04)	1.09 (1-1.18)
New Territories East Cluster	0.9 (0.84-0.95)	0.97 (0.88-1.06)
Kowloon West Cluster	0.92 (0.88-0.98)	1.13 (1.04-1.22)
Kowloon East Cluster	0.9 (0.85-0.95)	1.03 (0.95-1.12)
Kowloon Central Cluster	1.0 (0.94-1.06)	1.17 (1.07-1.28)

Nursing home residency, n (%)	1.6 (1.54-1.65)	1.68 (1.6-1.77)
Seasonal influenza / Pneumococcal vaccination, n (%)	1.03 (0.97-1.08)	1.03 (0.95-1.12)
Surgical operation for hip fracture, n (%)	0.81 (0.78-0.85)	0.75 (0.7-0.8)
Frequency of healthcare service in past one year, mean±sd		
In-patient admission	1.02 (1.01-1.02)	1.01 (1.01-1.02)
Out-patient clinics	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Intensive care units	1.1 (0.98-1.23)	1.01 (0.85-1.22)
Medical history, n (%)		
Coronary heart disease	1.07 (1.02-1.13)	1.05 (0.97-1.14)
Congestive heart failure	1.13 (1.07-1.19)	1.13 (1.04-1.22)
Arrhythmia and conduction disorders	1.13 (1.08-1.19)	1.11 (1.03-1.19)
Arterial disease	1.07 (1-1.15)	1.11 (1-1.24)
Hypertensive disease	1.0 (0.97-1.04)	1.01 (0.95-1.06)
Cerebrovascular disease	1.12 (1.08-1.17)	1.08 (1.01-1.15)
Chronic obstructive pulmonary disease	1.23 (1.16-1.3)	1.14 (1.05-1.25)
Other lung diseases	1.65 (1.58-1.71)	1.1 (1.04-1.17)
Diabetes	1.13 (1.07-1.19)	1.22 (1.12-1.32)
Hyperlipidemia	0.97 (0.91-1.03)	0.91 (0.83-1.0)
Obesity	0.75 (0.54-1.04)	0.52 (0.28-0.97)
Renal failure	1.22 (1.14-1.31)	1.27 (1.15-1.4)
Chronic liver disease	1.36 (1.15-1.61)	1.46 (1.13-1.87)
Osteoporosis	1.09 (1.02-1.16)	1.14 (1.03-1.25)
Fall	0.9 (0.82-0.99)	0.82 (0.72-0.94)
Other major fractures	1.03 (0.99-1.08)	1.09 (1.02-1.17)
Connective tissue disease	1.35 (1.14-1.6)	1.21 (0.92-1.61)
Dementia	1.13 (1.07-1.19)	1.19 (1.1-1.28)
Thyroid disorders	1.06 (0.97-1.16)	1.1 (0.96-1.26)
Prescription in past 180 days, n(%)		
Digoxin	1.15 (1.06-1.25)	1.32 (1.18-1.48)
Loop diuretics	1.25 (1.2-1.32)	1.22 (1.14-1.3)
Other diuretics	0.99 (0.94-1.05)	0.94 (0.86-1.02)

Anti-arrhythmics class I and II	1.08 (0.97-1.2)	1.24 (1.07-1.43)
Beta blockers	1.02 (0.98-1.06)	0.98 (0.93-1.04)
Angiotensin receptor blocker/ angiotensin converting enzyme inhibitor/ renin inhibitor	0.99 (0.95-1.03)	0.98 (0.93-1.04)
Nitrates	0.95 (0.9-1.01)	0.92 (0.85-1.0)
Calcium channel blockers	1.02 (0.98-1.05)	1.04 (0.99-1.09)
Peripheral vasodilators	1.1 (1-1.21)	1.15 (1.01-1.32)
Anticoagulants	1.0 (0.94-1.06)	0.94 (0.86-1.03)
Platelet inhibitors	1.07 (1.03-1.12)	1.09 (1.02-1.15)
Lipid regulating drugs	0.85 (0.81-0.9)	0.8 (0.74-0.87)
Antipsychotics	1.4 (1.33-1.46)	1.38 (1.29-1.47)
Antidepressants	1.08 (1.03-1.14)	1.05 (0.98-1.13)
Antidiabetic drugs	1.0 (0.95-1.06)	0.93 (0.85-1.01)
Oral corticosteroids	1.26 (1.18-1.35)	1.21 (1.09-1.33)
Non-steroidal anti-inflammatory drugs	0.86 (0.82-0.91)	0.77 (0.71-0.84)
Proton pump inhibitors	1.1 (1.05-1.15)	1.14 (1.07-1.22)
Beta2 agonists	1.23 (1.15-1.3)	1.18 (1.08-1.28)
Inhaled corticosteroids	1.05 (0.96-1.13)	0.89 (0.79-1.0)
Immunosuppressant	1.02 (0.66-1.6)	1.35 (0.69-2.62)

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^Cox regression model adjusted for all covariates used in the propensity score model shown in table 1

\*N-BPs nitrogen-containing bisphosphonates

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